DISCLOSURES

Antonio Cuneo

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Gilead					X	X	
Janssen					X	X	
Roche					X	X	
Abbvie					X	X	
Sandoz					X		
Mundipharma					X		
Novartis					X		
BMS					X		
Amgen						X	

AGGIORNAMENTI IN EMATOLOGIA
FAENZA,
Hotel Vittoria
7 Giugno 2018

Responsabile Scientifico
Francesco Lanza

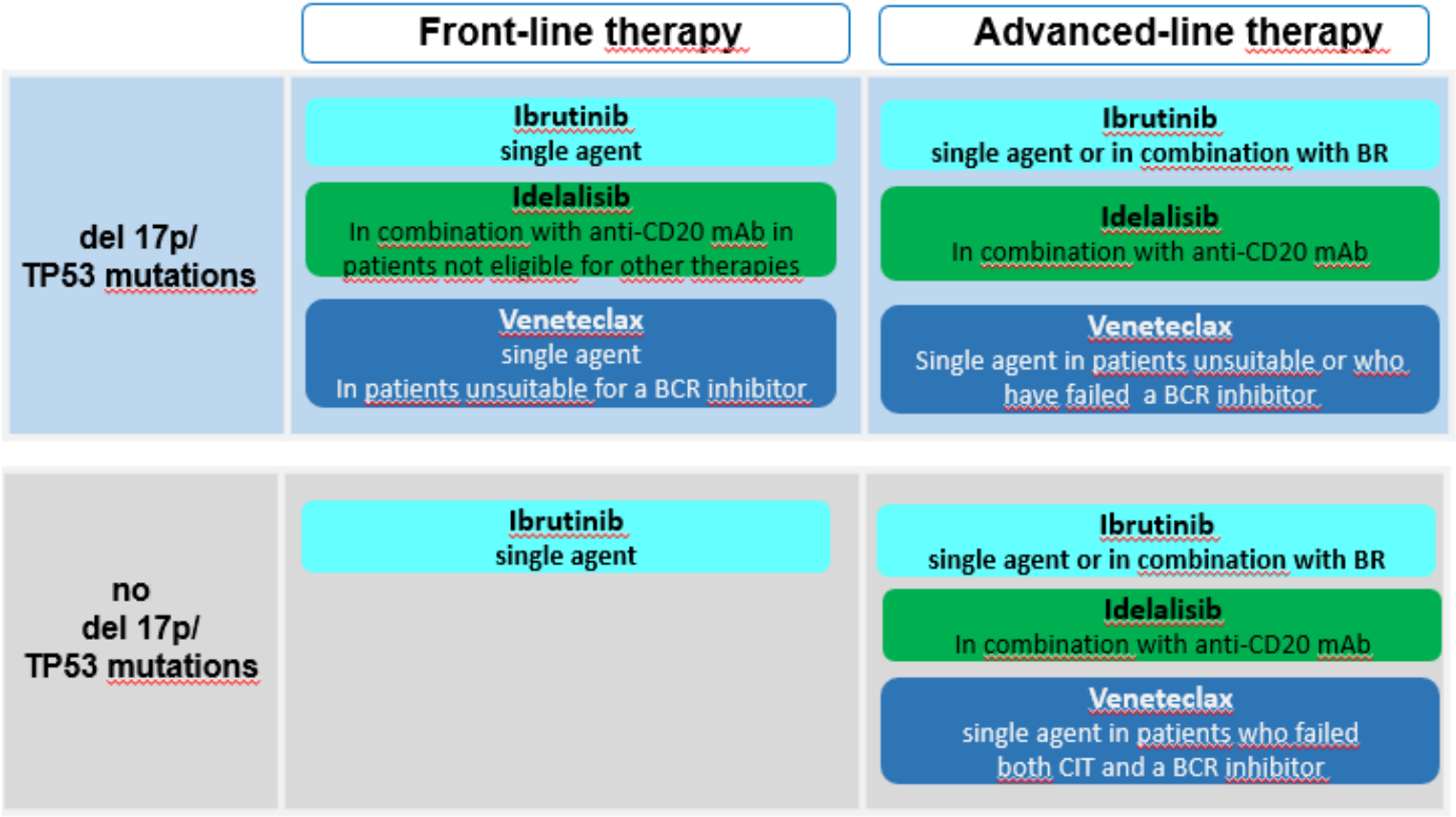
Leucemia linfatica cronica: ruolo dei farmaci di nuova generazione

- **Established indications**
  1) trials
  2) real life

- **New combinations**

università di ferrara
DA SEICENTO ANNI GUARDIAMO AVANTI.
Prof. Antonio Cuneo, MD, PhD

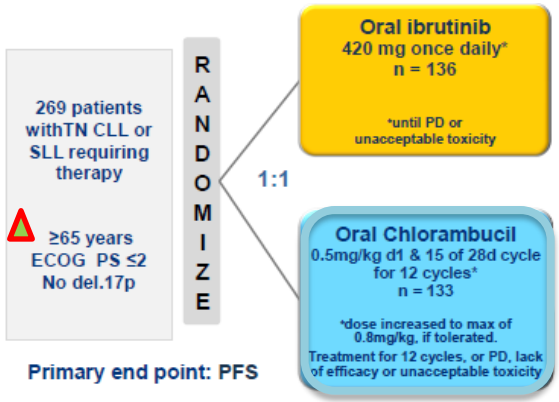
EMA indications: BCR and BCL2 inhibitors for patients with CLL



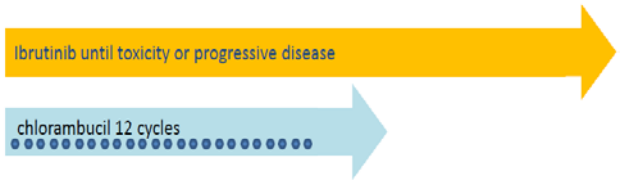
Courtesy of Francesca Mauro – Hematology «la Sapienza, Rome

EMA website. 2017 Imbruvica SmPC.
EMA website. 2017 Zydelig SmPC.
EMA website. 2017 Venclyxto SmPC.

Phase III RESONATE-2: Frontline Ibrutinib vs Chlorambucil in Elderly Patients With CLL



* ibrutinib for patients progressing on chlorambucil



Baseline Characteristics

	Ibrutinib (N=136)	Chl (N=133)
Median age, years (range)	73 (65-89)	72 (65-90)
≥70 years	96 (71%)	93 (70%)
ECOG PS 2	60 (44%)	54 (41%)
CIRS >6	42 (31%)	44 (33%)
CrCL <60ml/min	60 (44%)	67 (50%)
CLL	123 (90%)	126 (95%)
SLL	13 (10%)	7 (5%)
Rai stage III or IV	60 (44%)	62 (47%)
Bulky disease ≥5cm,	54 (40%)	40 (30%)
Del 11q22.3	29 (21%)	25 (19%)
Unmutated IGHV	58 (43%)	60 (45%)
Baseline cytopenias,	72 (53%)	73 (55%)

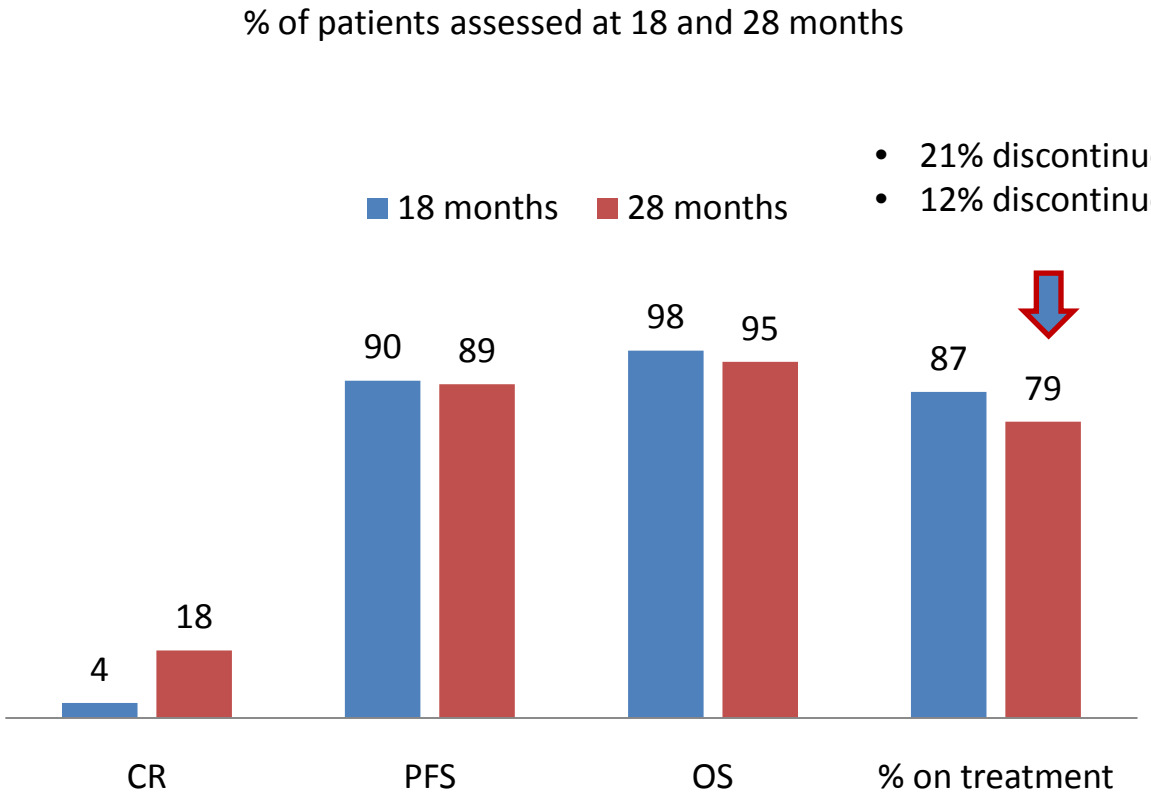
69% pts had
- CIRS >6 and/or
- Cr Cl <70 and/or
- ECOG 2

Patient Disposition

	Ibrutinib (N=136)*	Chl (N=133)*
Medi.duration of follow-up, months	18.4	
Med.duration of treatment (range), months	17.4 (0.7-24.7)	7.1 (0.5-11.7)
Patients completing max.12 CHL cycles	-	53 (40%)
Patients still on treatment at study closure	118	-
Patients on study follow up at study closure	131	114
Patients discontinued treatment	17	79
IRC confirmed disease progression	2	6
New anticancer therapy	0	4
Progressive disease	0	11
Lack of efficacy	0	21
Unacceptable toxicity/AE/death	14	30
Patient decision	1	6
Investigator decision	0	37
Other	0	1

Burger et al. , NEJM 2015; Tedeschi et al., ASH 2015, Barr P et al, ASH 2016

Efficacy and tolerability of ibrutinib is maintanied at 28 months in treatment naive CLL without 17p-



- 21% discontinued overall at 28 m.
- 12% discontinued due to AE

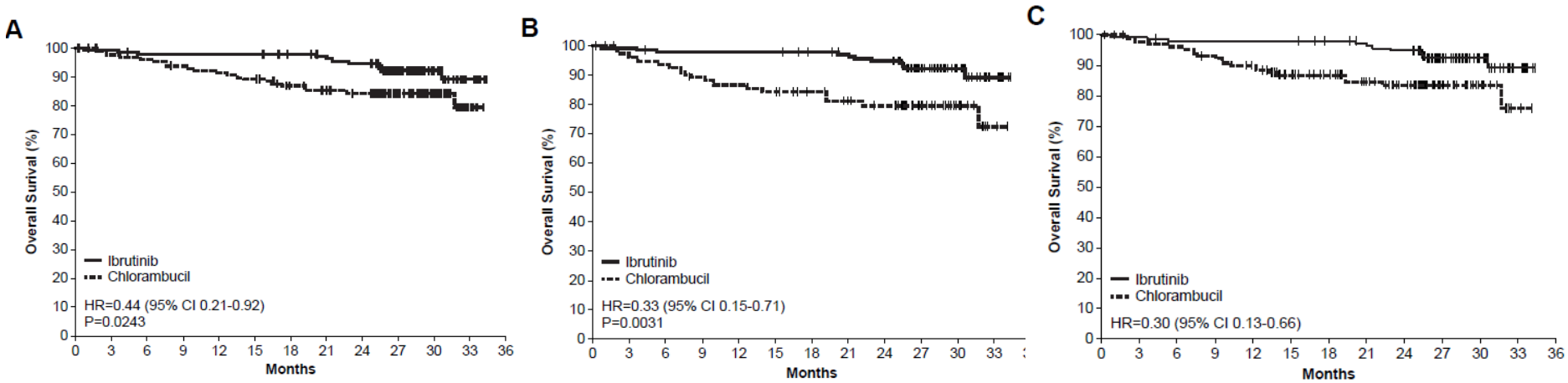
The data in the red columns were reported in Barr P, ASH 2016 abs# 234
The data in the blue columns were reported by Burger NEJM, 2015

Survival adjusting for crossover: phase 3 study of ibrutinib vs chlorambucil in older patients with untreated CLL: median f.u. 28 months

intent-to-treat population

excluding patients who crossed over to ibrutinib

rank-preserving structural failure time method



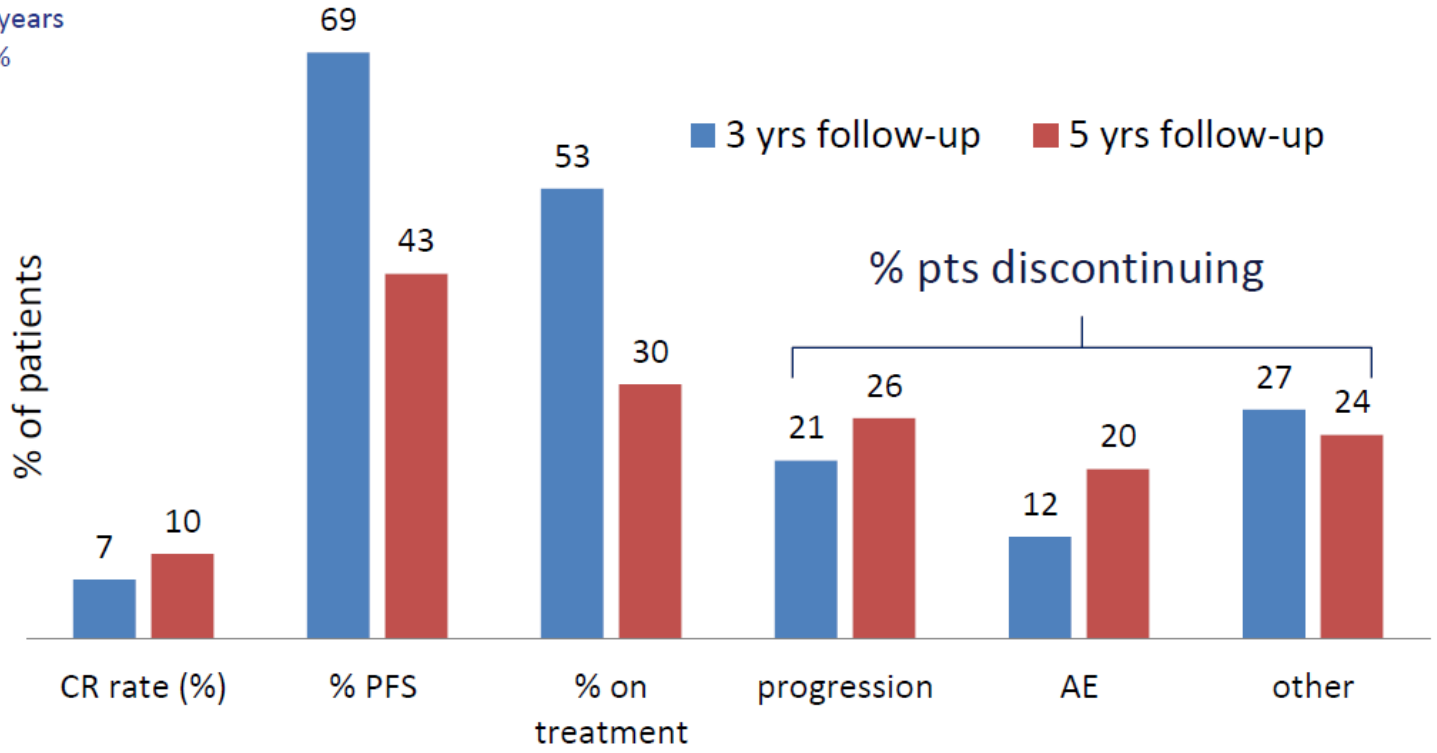
Kaplan-Meier curves of overall survival

Coutre SE et al. Haematologica. 2017 Nov 23

Experience with Single-Agent Ibrutinib in Patients with Relapsed/Refractory CLL/SLL at Three and Five-Years: *The baseline characteristics are important*

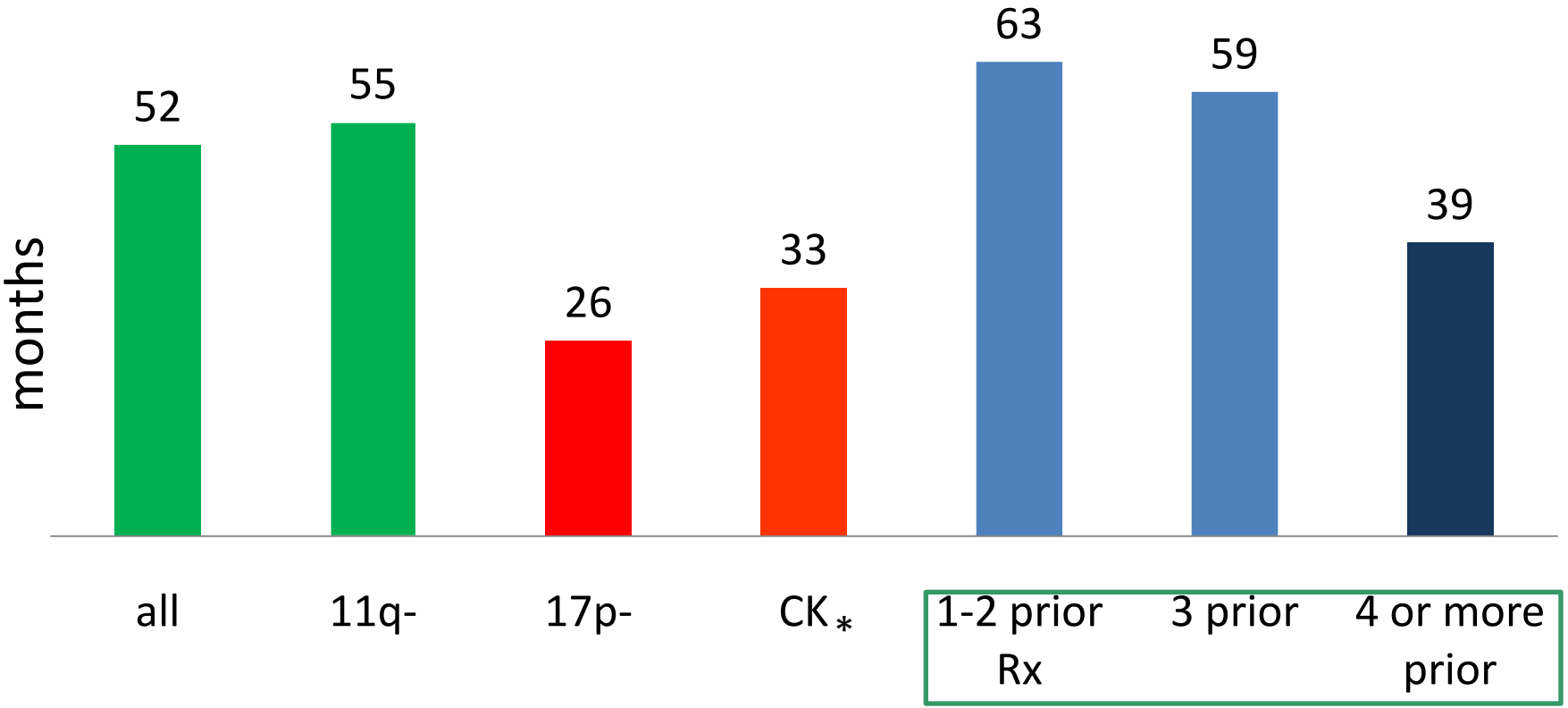
Efficacy and tolerability in 101 Rel/Ref CLL:

- ECOG 0-1: 96% pts
- Median age: 64 years
- ≥ 4 previous lines: 59%



Byrd JC, Blood 2015;
O'Brien ASH 2016 abs#233

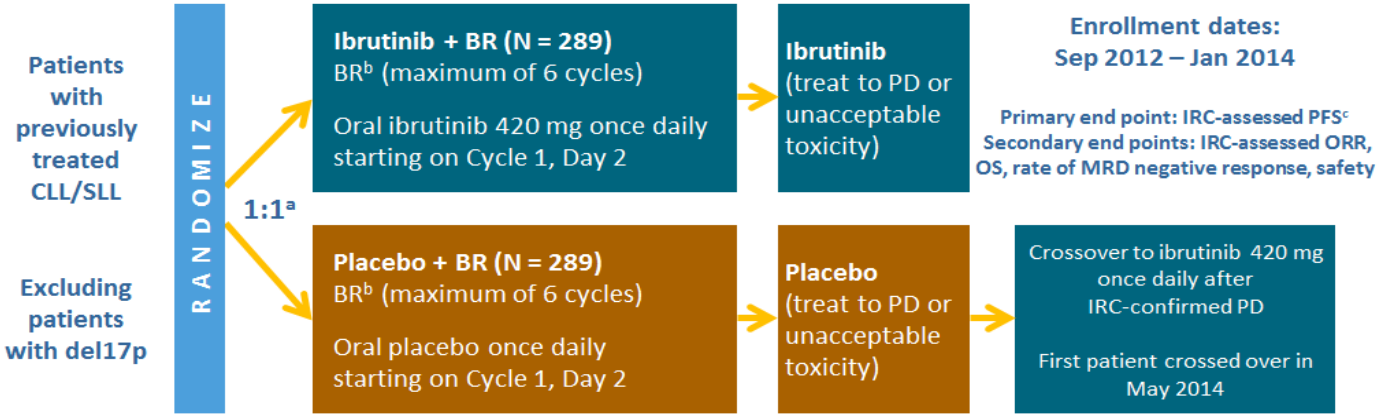
Median PFS in 101 rel/ref CLL under ibrutinib (5 yr follow-up) by genetics and previous treatment



*Not reached for non complex karyotype

Graphical elaboration from O'Brien ASH 2016 abs#233

Methods: HELIOS Study Design



Initial data report: Mar 2015
2-year update: Oct 2015

We now report the 2-year (25.4 months) follow-up data for:
- **Survival endpoints**
- **Response endpoints**
- **Minimum residual disease (MRD)**

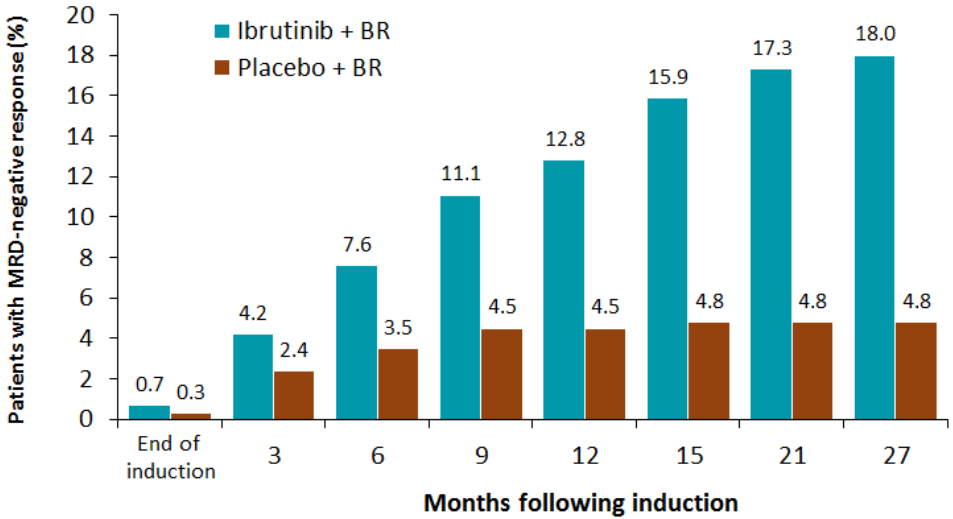
[a]Stratified by purine analogue refractory status (failure to respond or relapse in ≤ 12 months) and prior lines of therapy (1 line vs > 1 line).
[b]Similar dosing to Fischer K, et al. *J Clin Oncol.* 2011;29:3559-3566.
[c]According to 2008 iwCLL criteria (Hallek M, et al. *Blood.* 2008;111:5446-5456).

IRC, independent review committee; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival.

janssen Oncology
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Fraser et al. EHA 2016: Abstract S430 (Oral Presentation)

Results: MRD-Negative Response Over Time

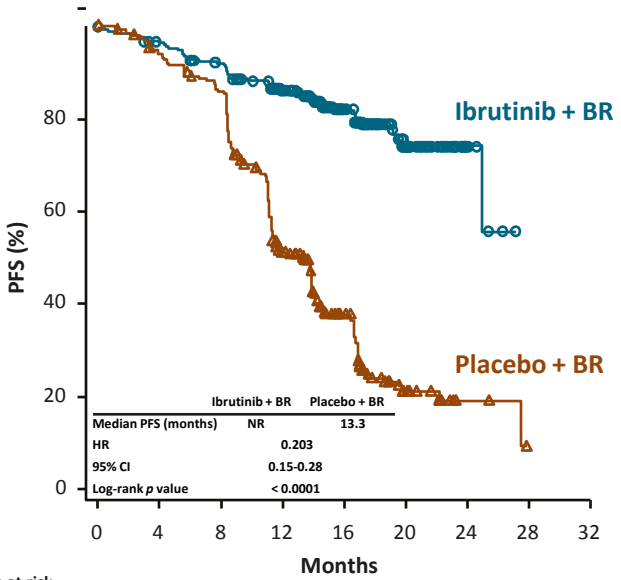


•MRD-negative response continues **to increase over time** for patients treated with ibrutinib + BR

Fraser et al. EHA 2016: Abstract S430 (Oral Presentation)

Results: PFS in the Intent-to-Treat Population

Median follow-up, 17 months
IRC-assessed

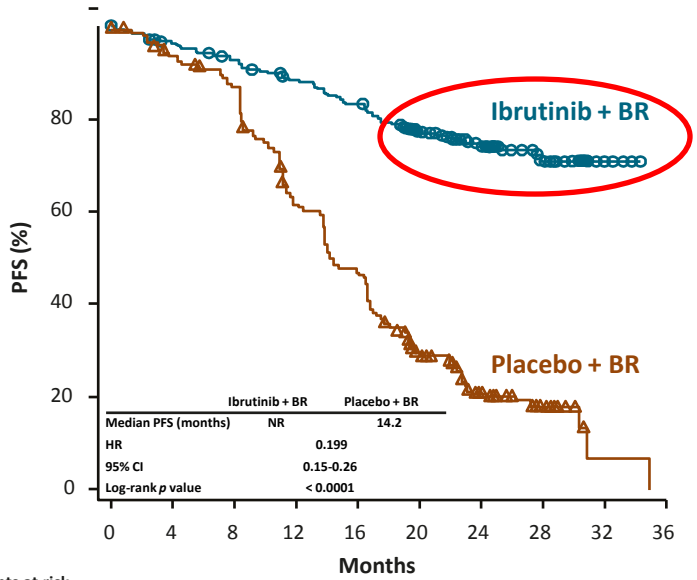


Patients at risk

Ibrutinib + BR	289	264	247	200	127	52	5	0	0
Placebo + BR	289	259	234	117	59	17	3	0	0

Chanan-Khan A, et al. *Lancet Oncol*. 2016;17:200-211.

Median follow-up, 25.4 months
Investigator-assessed



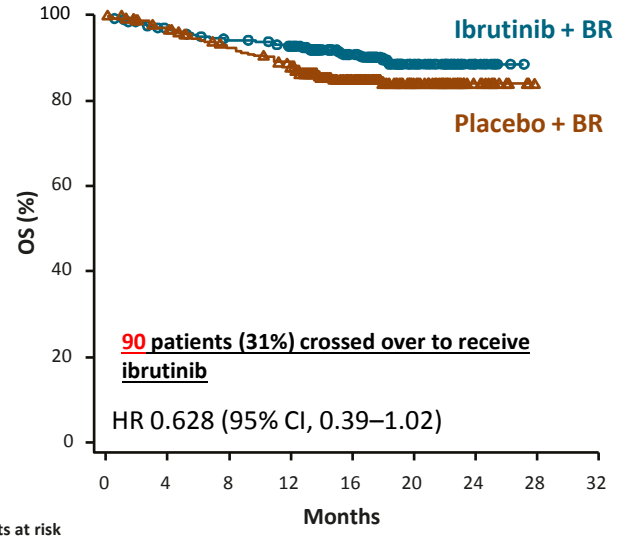
Patients at risk

Ibrutinib + BR	289	268	256	241	227	174	117	47	6	0
Placebo + BR	289	260	237	166	125	65	31	10	1	0

Fraser et al. EHA 2016: Abstract S430 (Oral Presentation)

Results: OS in the Intent-to-Treat Population

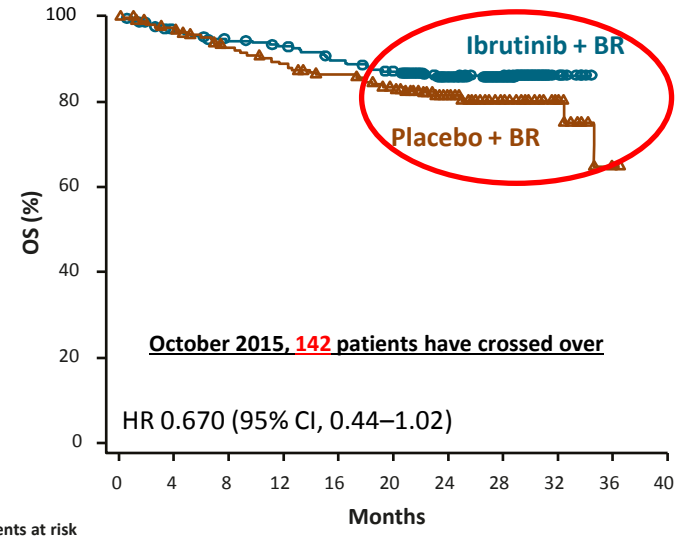
Median follow-up, 17 months



Patients at risk									
Ibrutinib + BR	289	273	261	250	147	73	8	0	0
Placebo + BR	289	273	255	237	138	70	16	0	0

Chanan-Khan A, et al. *Lancet Oncol*. 2016;17:200-211.

Median follow-up, 25.4 months



Patients at risk											
Ibrutinib + BR	289	273	261	255	244	233	147	74	14	0	0
Placebo + BR	289	273	255	244	234	219	138	71	21	2	0

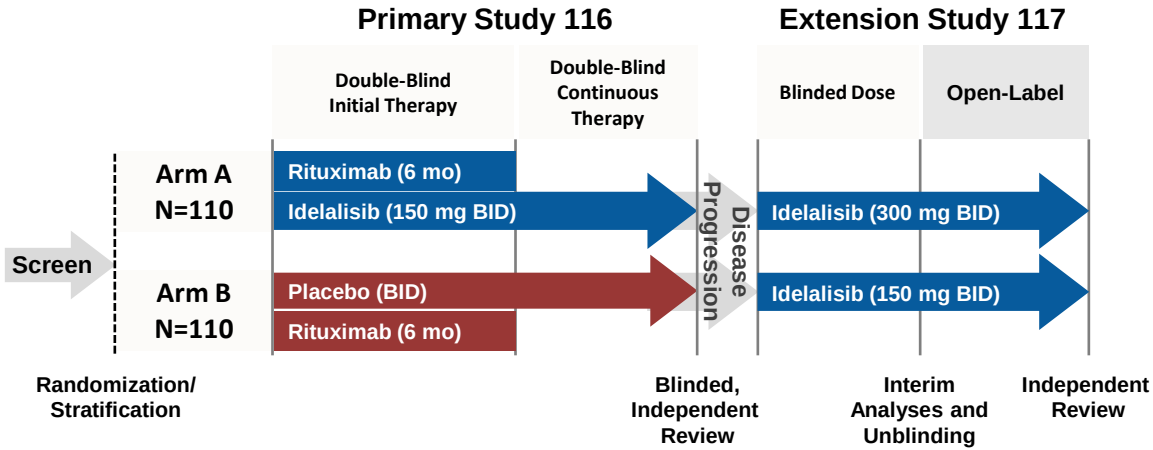
Fraser et al. EHA 2016: Abstract S430 (Oral Presentation)

Study GS-US-312-0116 (Phase 3)

Idelalisib and Rituximab in rel/ref

Population:

Relapsed CLL warranting treatment (iwCLL); progression < 24 mo since last treatment



	Median Follow-up, months		
	IDELA + R	PBO + R	
1st Interim Analysis	4	4	DMC halted trial (Furman NEJM 2014) 50% events
2nd Interim Analysis	6	5	Blind ended (Coutre ASCO 2014) 63% events • Arm A continues (amendment to be all 150mg) • Arm B crosses over
Update	13	11	PFS, OS by subgroup analysis

Furman R et al *NEJM* 2014;370:997-1007

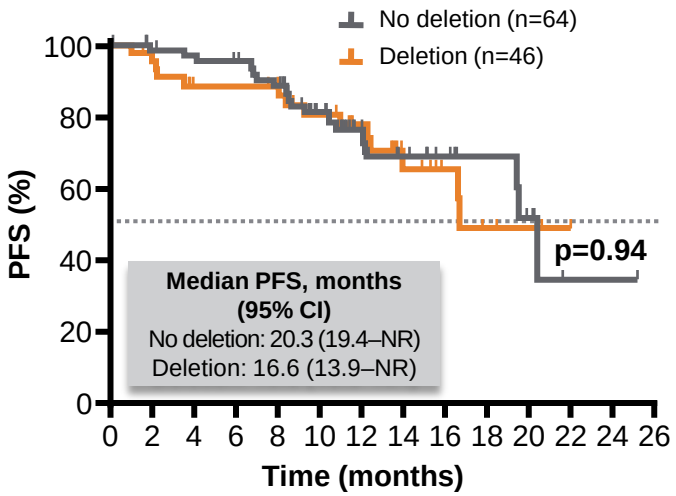
Patients included in Study 116 were elderly, had a poor performance status and cytopenias

	Typical relapsed CLL patient	Ibrutinib RESONATE population[3]	Zydelig + R Study 116 population[6]	Ofatumumab licensing study[4] (FA-ref/BF-ref)
Trial design	Registry	Open-label randomised	Double-blind placebo controlled	Non-randomised Phase II
Median age (years)	72.5[1a]	67	71	64/62
ECOG PS, 1–3 (%)	N/A	59	87	65
ECOG PS, 2–3 (%)	23.2[2b]	0	28	N/A
del(17p) and/or *TP53* mutation (%)	42[5]	33	43	29/18
Blood count criteria	N/A	Platelets ≥30 x 10^9/L Neutrophils ≥0.75 x 10^9/L	No restrictions 35% Grade 3 or 4 cytopenias	No blood counts or transfusion restrictions

Del(17p) or *TP53* prognostic factors do not impact on the efficacy of Zydelig + R

Second interim analysis: median PFS 19,4 months in the idela + R arm

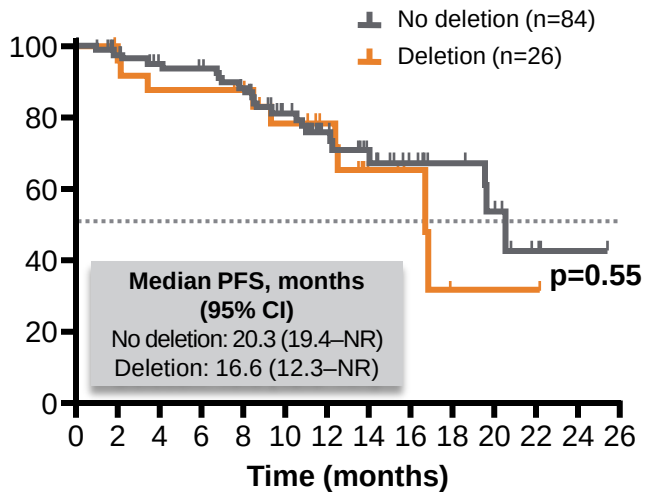
Del(17p)/*TP53* mutation



Number at risk

No del	64	61	59	59	52	37	21	14	11	8	4	1	1	1
Del	46	41	36	36	33	30	22	12	8	4	3	0	0	0

Del(17p)

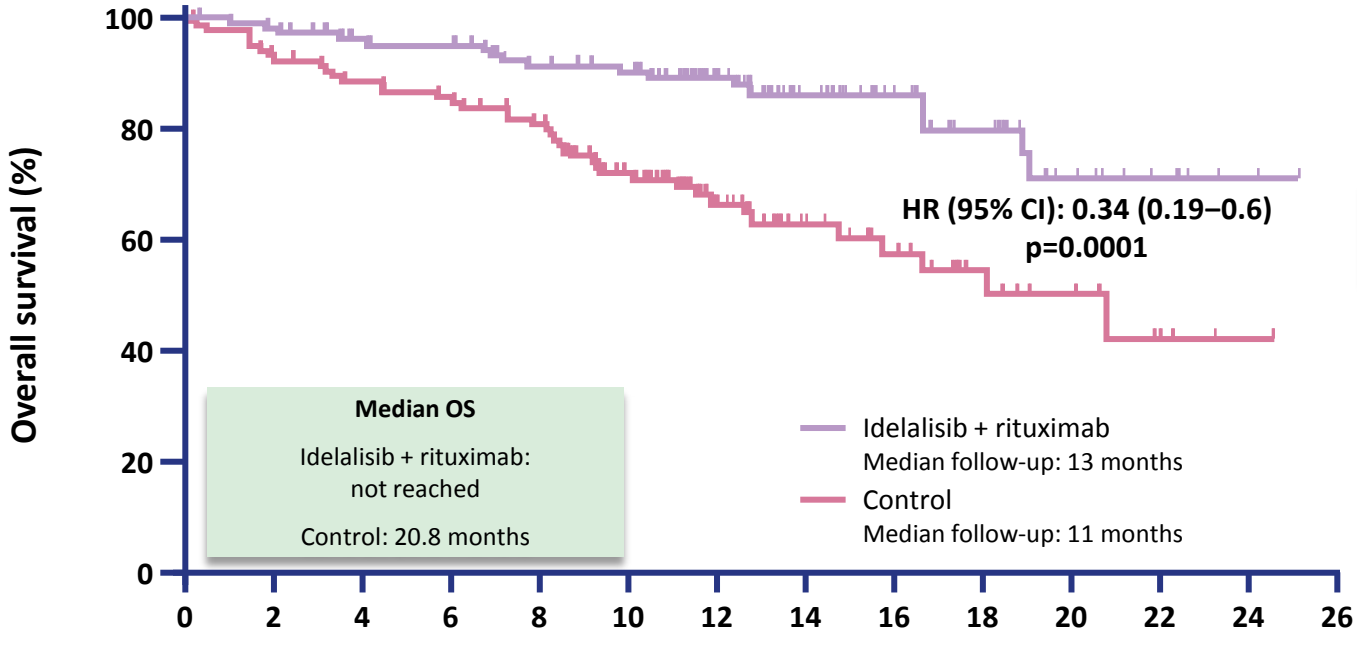


84	78	73	71	65	49	31	20	15	11	6	1	1	1
26	23	22	22	20	17	12	6	4	1	1	0	0	–

Sharman JP, *et al.* ASH 2014 (Abstract 330; oral presentation).

Difference in efficacy (OS) of Idelalisib + rituximab maintained despite crossover in the extension study

- Follow-up including extension study



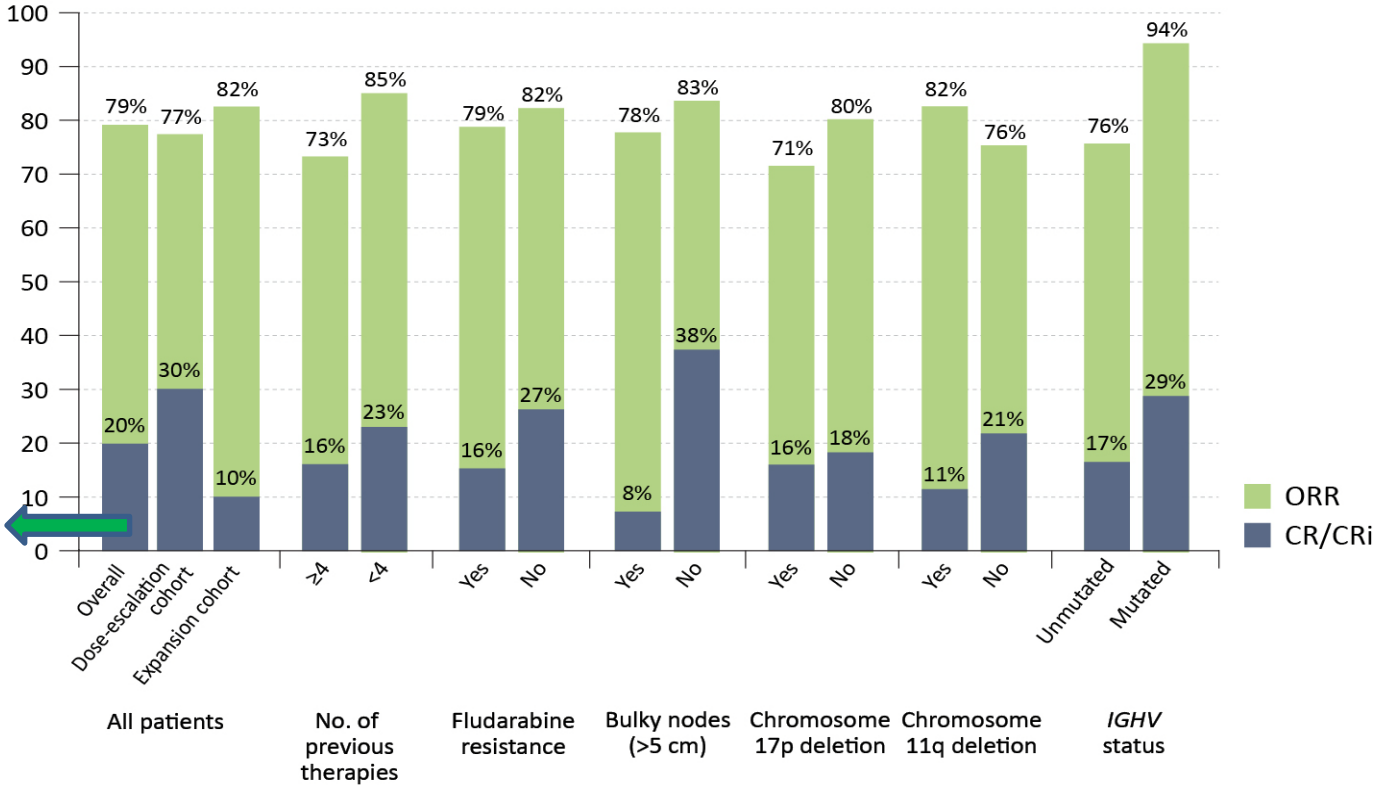
N at risk (events)														
Idelalisib + R	110	107	101	100	93	85	60	41	30	23	13	7	3	0
Placebo + R	110	99	93	90	84	66	42	27	20	13	8	4	1	0

As randomised, including crossover study

Sharman JP, *et al.* ASH 2014 (Abstract 330; oral presentation);
Munir, T., et al. (2015). British Journal of Haematology 169(Supplement s1): 19.

Phase 1, open-label multicenter dose escalation trial of Venetoclax

35% of CR are MRD- (5% of all pts)



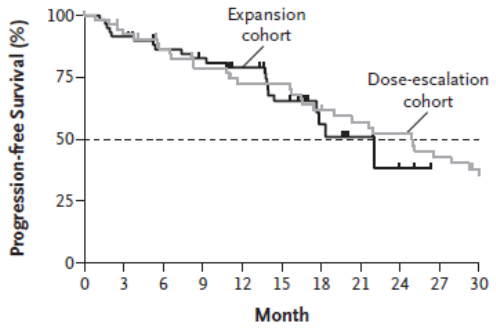
17/23 patients in CR/CRi had multicolor FC testing for **MRD** and 6 (**35%**) of those tested were negative by standard criteria (5% of all patients)

From: Roberts AW, et al. *N Engl J Med.* 2016;374(4):311-322.

Targeting BCL2 with Venetoclax in Relapsed Chronic Lymphocytic Leukemia

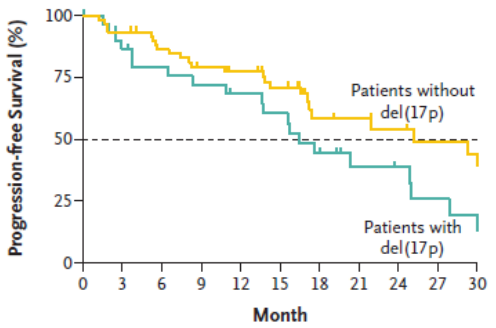
- **median duration of PFS of 25 months (95% CI, 17 to 30) in the dose-escalation cohort**
- **median follow-up duration in the expansion cohort , 17 months; range, <1 to 26).**
  estimated rate of progression-free survival at 15 months 66% (95% CI, 51 to 77)

A



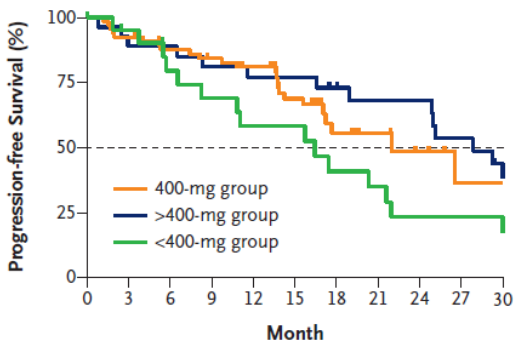
No. at Risk											
Expansion cohort	60	55	48	45	40	29	10	5	2		
Dose-escalation cohort	56	49	44	39	34	34	27	24	22	18	15

B



No. at Risk											
Patients without del(17p)	60	56	49	44	39	33	16	14	12	10	9
Patients with del(17p)	31	31	25	22	18	15	11	7	6	4	3

C



No. at Risk											
400-mg group	67	61	54	50	45	34	14	9	6	3	3
>400-mg group	27	24	23	21	19	19	16	14	14	11	8
<400-mg group	22	19	15	13	10	10	7	5	4	4	4

Roberts AW, et al. *N Engl J Med.* 2016;374(4):311-322.

AGGIORNAMENTI IN EMATOLOGIA
FAENZA,
Hotel Vittoria
7 Giugno 2018

Responsabile Scientifico
Francesco Lanza

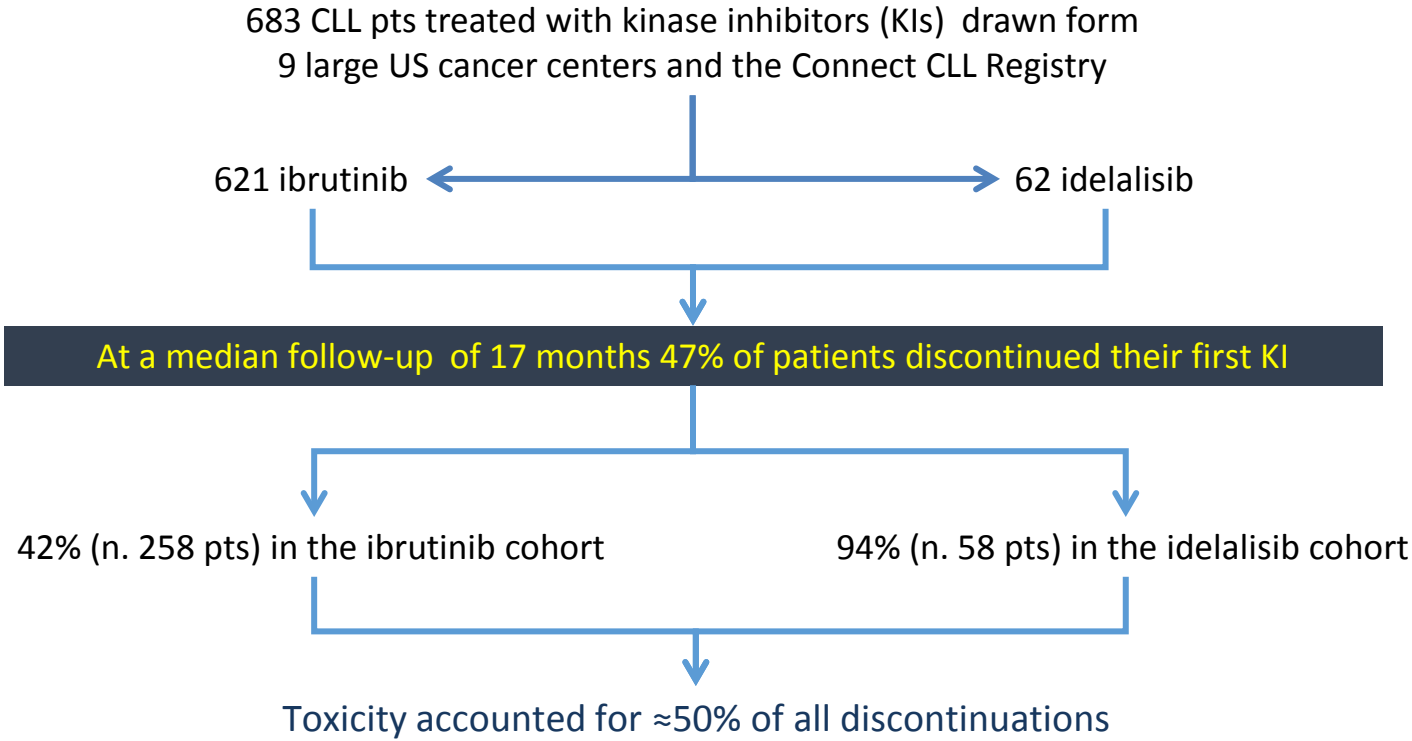
Leucemia linfatica cronica: ruolo dei farmaci di nuova generazione

- **Established indications**
  1) trials
  2) real life

- **New combinations**

università di ferrara
DA SEICENTO ANNI GUARDIAMO AVANTI.
Prof. Antonio Cuneo, MD, PhD

683 CLL pts treated with kinase inhibitors (KIs) drawn form 9 large US cancer centers and the Connect CLL Registry



Mato A et al, Ann Oncol. 2017 May 1;28(5):1050-1056. doi: 10.1093/annonc/mdx031

5 Most Common Toxicities as a Reason for Discontinuation

"Kinase Inhibitor Intolerant" patients (median f.u. 17 months)

683 CLL pts treated with kinase inhibitors (KIs) drawn form 9 large US cancer centers and the Connect CLL Registry

Ibrutinib (n. 258 pts = 42% of the cohort)	**Idelalisib (n. 58 pts = 94% of the cohort)**
Atrial fibrillation (18 pts)	Pneumonitis (7 pts)
Infection (13 pts)	Diarrhea/Colitis (6 pts)
Pneumonitis (12 pts)	Rash (5 pst)
Bleeding (11pts)	Transaminitis (4 pts)
Arthralgia (9 pts)	Infection (2 pts)

Mato A et al, Ann Oncol. 2017 May 1;28(5):1050-1056. doi: 10.1093/annonc/mdx031

Integrated Safety Analysis of Venetoclax Monotherapy in CLL

Event, n (%)	All Patients N=296	Pts with del(17p) n=188	BCRi Failures (n=94)
Any Grade AE	293 (99)	185 (98)	94 (100)
Common AEs, all Grades (≥20% of all patients)			
Neutropenia	120 (41)	75 (40)	33 (35)
Diarrhea	115 (39)	71 (38)	33 (35)
Nausea	106 (36)	60 (32)	30 (32)
Anemia	87 (29)	52 (28)	35 (37)
Fatigue	77 (26)	44 (23)	26 (27)
Upper respiratory tract infection	68 (23)	35 (19)	10 (11)
Grade 3/4 AEs	225 (76)	142 (76)	67 (71)
Common Grade 3/4 AEs (≥10% of all patients)			
Neutropenia	110 (37)	69 (37)	29 (31)
Anemia	45 (15)	27 (14)	18 (19)
Thrombocytopenia	40 (14)	29 (15)	14 (15)
AEs Leading to[a]			
Discontinuation	27 (9)	20 (11)	7 (7)
Interruption of venetoclax	103 (25)	58 (31)	27 (29)
Venetoclax dose adjustment	35 (12)	24 (13)	8 (9)
Death	12 (4)	9 (5)	7 (7)

[a]Excludes those due to disease progression.

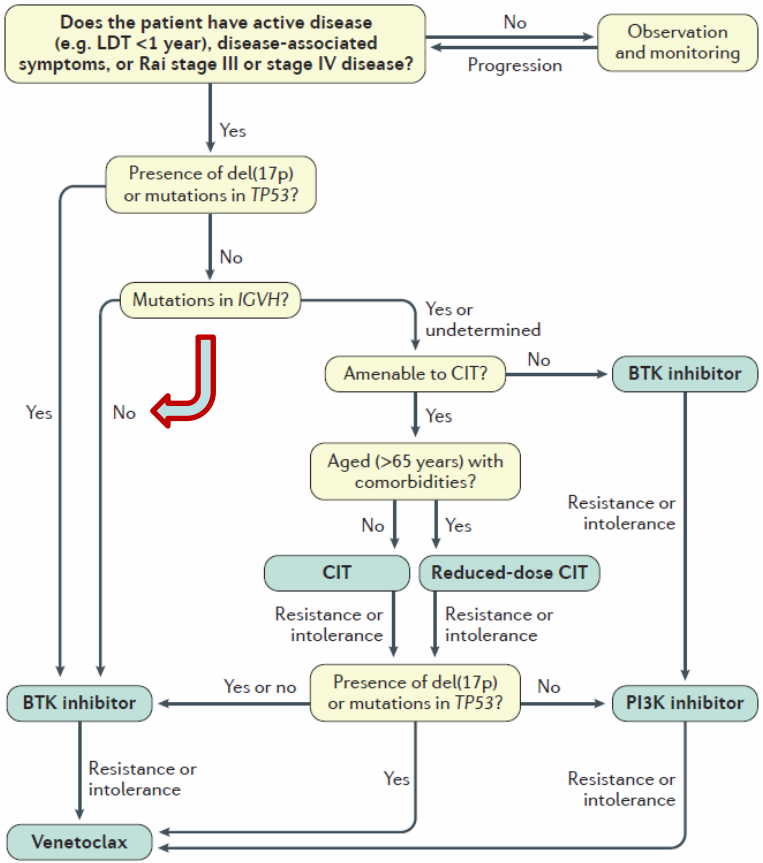
Davids MA, EHA 2016

Different views on first line treatment of CLL

	No *TP53* aberration	*TP53* aberration
Physically fit	Fludarabine plus cyclophosphamide plus rituximab (age ≤65 years); or bendamustine plus rituximab (age >65 years)	Ibrutinib or idelalisib plus rituximab or venetoclax (if ibrutinib therapy is not suitable because of comorbidities or comedication)
Physically unfit	Chlorambucil plus obinutuzumab; or chlorambucil plus ofatumumab; or chlorambucil plus rituximab; or ibrutinib monotherapy	Ibrutinib or idelalisib plus rituximab or venetoclax (if ibrutinib is not suitable because of comorbidities or comedication)

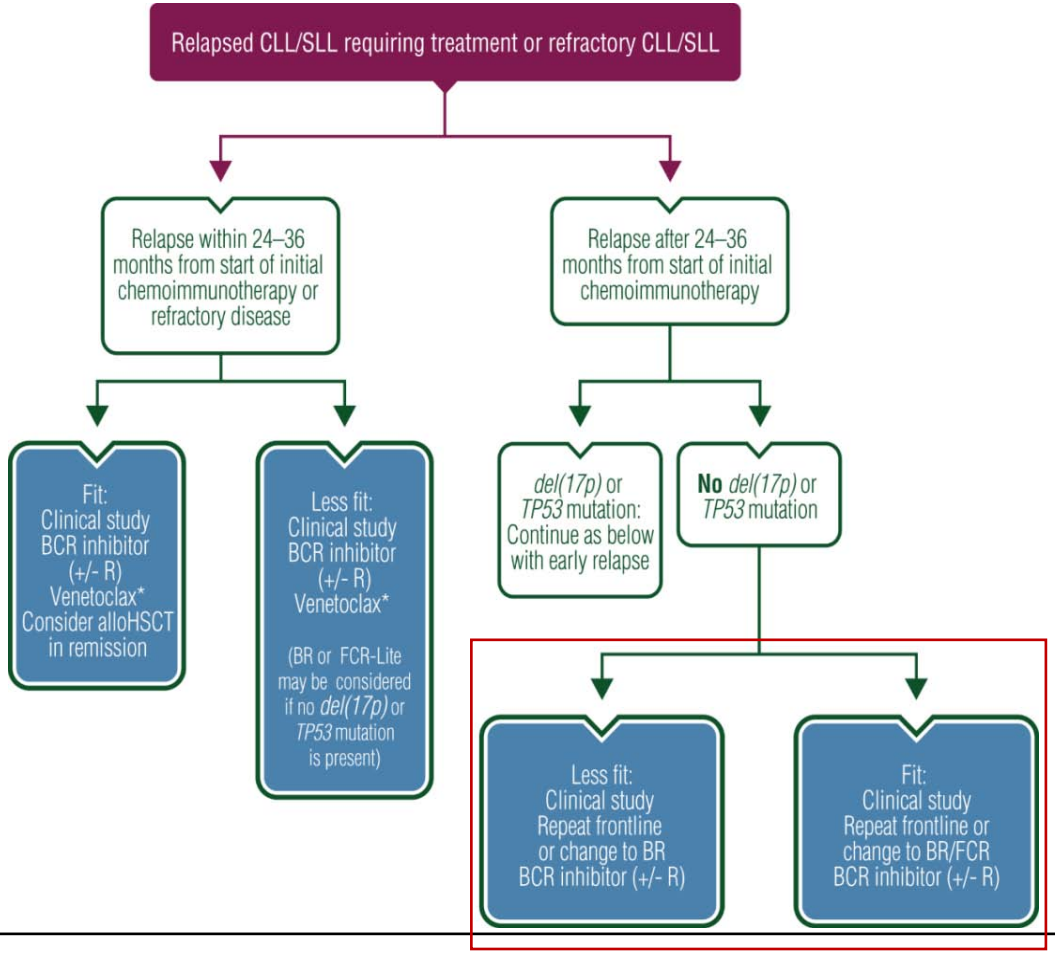
Table 2: First-line treatment of chronic lymphocytic leukaemia in physically fit and physically unfit patients

Hallek M, Shanafelt TD, Eichhorst B - Lancet 2018; 391:1524-1537



Kipps T, Stevenson F, Wu KJ, Croce CM, Packham G, Wierda W, O'Brien S, Gribben J, Rai K Nat Rev Dis Primers. 2017 Feb 9;3:17008

ESMO Guidelines For R/R CLL



From: Appendix 4: Chronic lymphocytic leukaemia: eUpdate published online 27 June 2017 (www.esmo.org/Guidelines/Haematological-Malignancies)
Ann Oncol. 2017;28(suppl_4):iv149-iv152. doi:10.1093/annonc/mdx242

Different views on first salvage treatment of CLL

	Standard therapy	Alternative therapies
Refractory or progression within 3 years		
Physically fit	Ibrutinib possibly followed by allogeneic haemopoietic stem-cell transplant	Idelalisib plus rituximab; venetoclax; lenalidomide
Physically unfit	Change therapy	Ibrutinib; idelalisib plus rituximab; venetoclax; lenalidomide; CD20 antibody alone
Progression after 3 years		
All fitness levels	Repeat front-line therapy	Change to another chemoimmunotherapy; ibrutinib; idelalisib plus rituximab

Table 3: Second-line treatment of chronic lymphocytic leukaemia, by response to first-line treatment and fitness

Hallek M, Shanafelt TD, Eichhorst B - Lancet 2018; 391:1524-1537

NCCN Guidelines For R/R CLL

NCCN Guidelines® Insights

Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia, Version 1.2017

Featured Updates to the NCCN Guidelines

Relapsed/Refractory Therapy

Frail patient with significant comorbidity or age ≥65 y and younger patients with significant comorbidities

- Ibrutinib[c] (category 1)
- Idelalisib + rituximab[c,h] (category 1)
- Idelalisib[c]
- Venetoclax[i,j]
- Chemoimmunotherapy
  - ◊ Bendamustine ± rituximab
  - ◊ Reduced-dose FCR[e,f]
  - ◊ Reduced-dose PCR
  - ◊ High-dose methylprednisolone (HDMP) + rituximab
  - ◊ Rituximab + chlorambucil
  - ◊ Ibrutinib,[c] bendamustine, rituximab (category 3)
  - ◊ Idelalisib,[c] bendamustine, rituximab (category 3)
- Ofatumumab
- Obinutuzumab
- Lenalidomide[k] ± rituximab
- Alemtuzumab[l] ± rituximab
- Dose-dense rituximab (category 2B)

CLL/SLL without del(17p)/*TP53* mutation

Relapsed/Refractory Therapy

- Age <65 y without significant comorbidities
  - Ibrutinib[c] (category 1)
  - Idelalisib + rituximab[c,h] (category 1)
  - Idelalisib[c]
  - Venetoclax[i,j]
  - Chemoimmunotherapy
    - ◊ FCR[e,f]
    - ◊ FC + ofatumumab
    - ◊ PCR
    - ◊ Bendamustine ± rituximab
    - ◊ RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)
    - ◊ OFAR[e] (oxaliplatin, fludarabine,[f] cytarabine, rituximab)
    - ◊ Ibrutinib,[c] bendamustine, rituximab (category 2B)
    - ◊ Idelalisib,[c] bendamustine, rituximab (category 2B)
  - Ofatumumab
  - Obinutuzumab
  - Lenalidomide[k] ± rituximab
  - Alemtuzumab[l] ± rituximab
  - HDMP + rituximab

Second-line Extended Dosing

- Ofatumumab maintenance (for complete or partial response after relapsed or refractory therapy) (category 2B)

See Suggested Regimens for CLL/SLL with del(17p) (3 of 5)

Consider prophylaxis for tumor lysis syndrome (See CSLL-C)

See monoclonal antibody and viral reactivation (See CSLL-C)

Wierda WG, et al, Natl Compr Canc Netw 2017;15(3):293–311

Is there a role for chemoimmunotherapy as first salvage treatment in CLL? Efficacy of Bendamustine and rituximab in a real-world patient population

Efficacy of bendamustine and rituximab as first salvage treatment in CLL and indirect comparison with ibrutinib: a GIMEMA, ERIC and UK CLL FORUM study

237 pts treated with BR (2nd line)
Median age 70 y

Median follow-up 37,1 months

median PFS: 25 m

Median OS: 74 m

Multivariable analysis

Parameters	P	Hazard Ratio	95% C.I.	
17p- vs others	0.0004	2.92	1.631	5.296
IGVH mut/unmut	0.0299	0.53	0.299	0.94
Others vs Binet C	0.0192	0.536	0.319	0.903

Parameters	P	Hazard Ratio	95% C.I.	
Stage A-B vs C	0,0276	0,547	0,320	0,935
CR+PR vs NR	0.0001	0.344	0.198	0.595

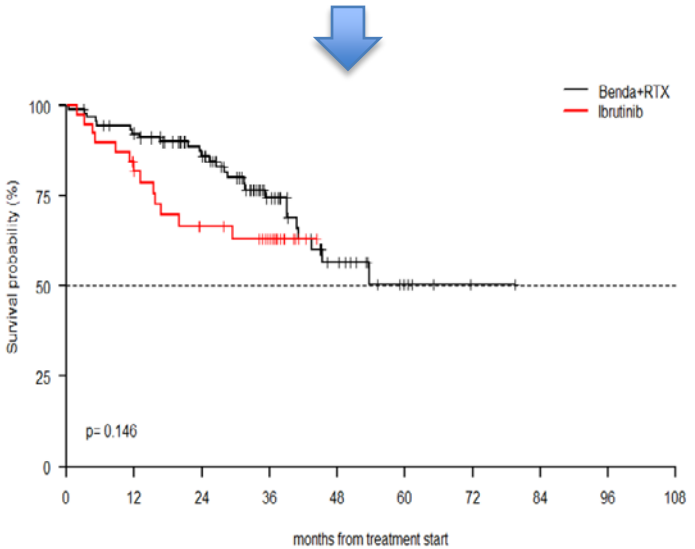
Cuneo A et a. Haematologica April 2018. Accepted

Is there a role for chemoimmunotherapy as first salvage treatment in CLL? Indirect comparison of BR and ibrutinib in a real-world population

Baseline characteristics of the BR and the ibrutinib cohorts (UK + NPP GIMEMA) in patients treated with chemoimmunotherapy in first line

Variable	BR (n=137)	Ibrutinib (n=71)	p
Median age years (range)	68.2 (39.4-84.6)	67.1 (27.5-85.3)	0.603
Age years (%) ≤65/>65	39 (34.5)/74 (65.5)	27 (38.6)/43 (61.4)	0.691
Gender (%) M/F	91 (66.4)/46 (33.6)	45 (63.4)/ 26 (36.6)	0.777
ECOG PS (%) 0-1/≥2	113 (91.9)/10 (8.1)	57 (82.6)/ 12 (17.4)	0.090
Months between 1st line and 2nd line			
median (range)	30.60 (0.40, 79.40)	19.40 (1.80, 77.60)	0.001
n. <36/≥36 (%)	81 (59.1)/56 (40.9)	54 (76.1)/17 (23.9)	0.023
Response to 1st line treatment (%) no/yes	28 (20.4)/109 (79.6)	8 (15.1)/45 (84.9)	0.524
IGHV (%)mutated/unmutated	17 (19.5)/70 (80.5)	8 (32.0)/17 (68.0)	0.295
17p- (%) yes/no	16 (14.8)/92 (85.2)	22 (36.1)/39 (63.9)	0.003

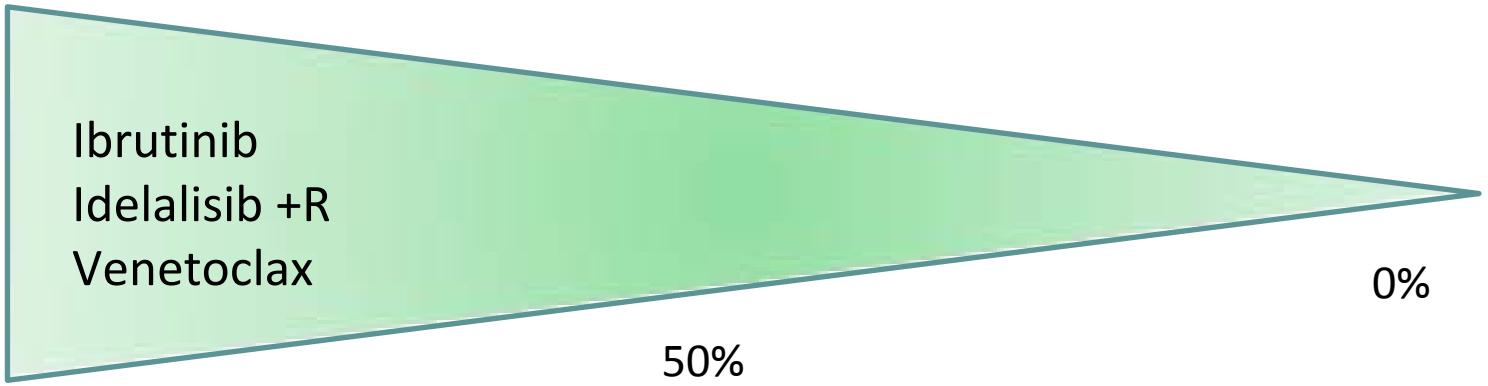
OS in 39 patients treated second-line with ibrutinib and in 92 patients treated with second line BR.
All patients had intact 17p and received CIT front-line



Cuneo A et a. Haematologica April 2018. Accepted

Risk-adapted options for treatment of CLL

N. of patients using mechanism-based treatment



TP53 disruption any line
Refractory disease
2nd line and Short PFS
≥3 line

2nd line and
- *IGHV* unmutated
- Complex karyotype
1st line and unfavourable prognostic markers

1st line
- standard risk

Cuneo A, personal view,.

AGGIORNAMENTI IN EMATOLOGIA
FAENZA,
Hotel Vittoria
7 Giugno 2018

Responsabile Scientifico
Francesco Lanza

Leucemia linfatica cronica: ruolo dei farmaci di nuova generazione

- **Established indications**
  1) trials
  2) real life

- **New combinations**

università di ferrara
DA SEICENTO ANNI GUARDIAMO AVANTI.
Prof. Antonio Cuneo, MD, PhD

Venetoclax Plus Rituximab Is Superior to Bendamustine Plus Rituximab in Patients with Relapsed/ Refractory CLL: Results from Pre-Planned Interim Analysis of the Randomized Phase 3 Murano Study

389 pts enrolled

- Ven + R (n=194) for a maximum of 2 yrs
- Benda + R (n=195) for 6 cycles

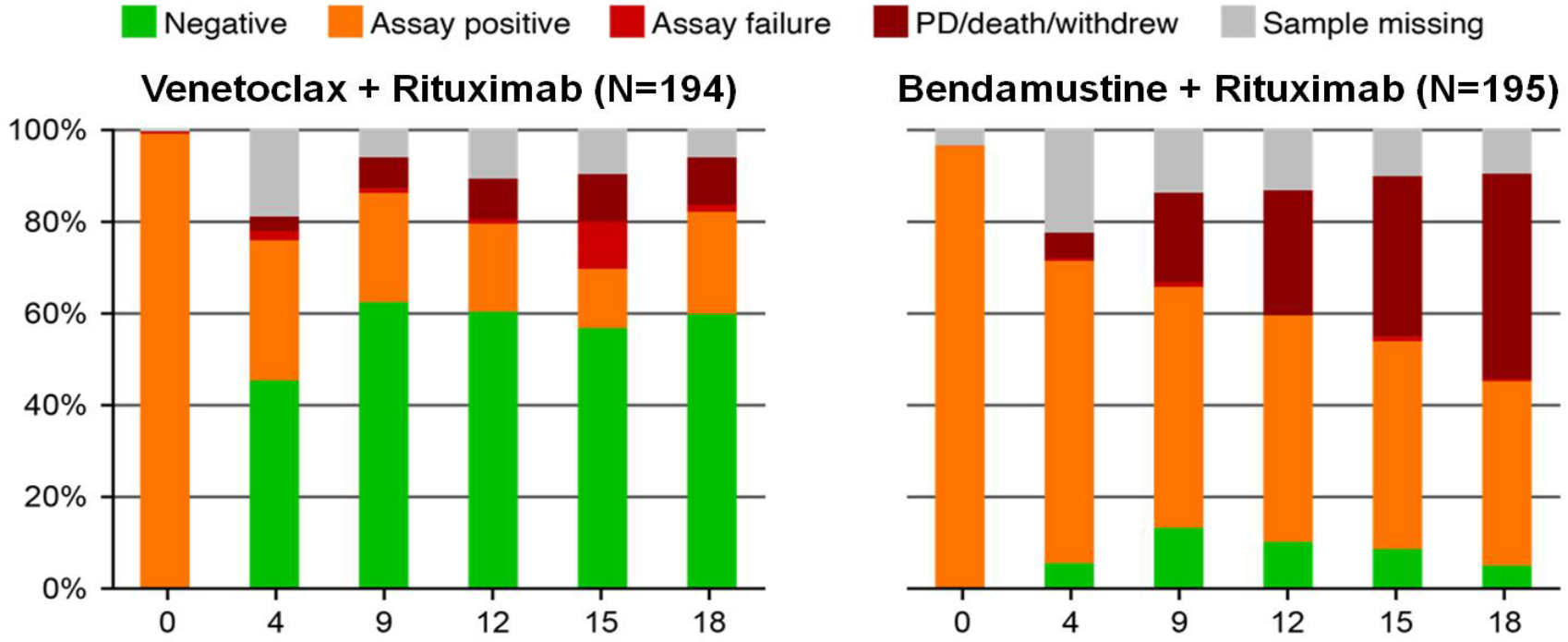
median follow-up 23.8 mo. [range 0.0–37.4]

Parameters	Ven + R (n=194)	Benda + R (n=195)
age	64.5 (28–83)	66.0 (22–85)
1 prior therapy	57.2%	60.0%
Prior purine analog	81%	81%
Prior rituximab	78%	76%
fludarabine refractory	14.1%	15.5%
del(17p)	26.6%	27.2%
ORR	93,3%	67,7%
CR/Cri*	26,8%*	8,2%
MRD-ve PB	83.5%	23.1%

*p<0.0001

Seymour JF et al, ASH 2017 LBA-2, adapted from the oral presentation

High Peripheral Blood MRD Negativity Rate Maintained Over Time for VenR vs. BR

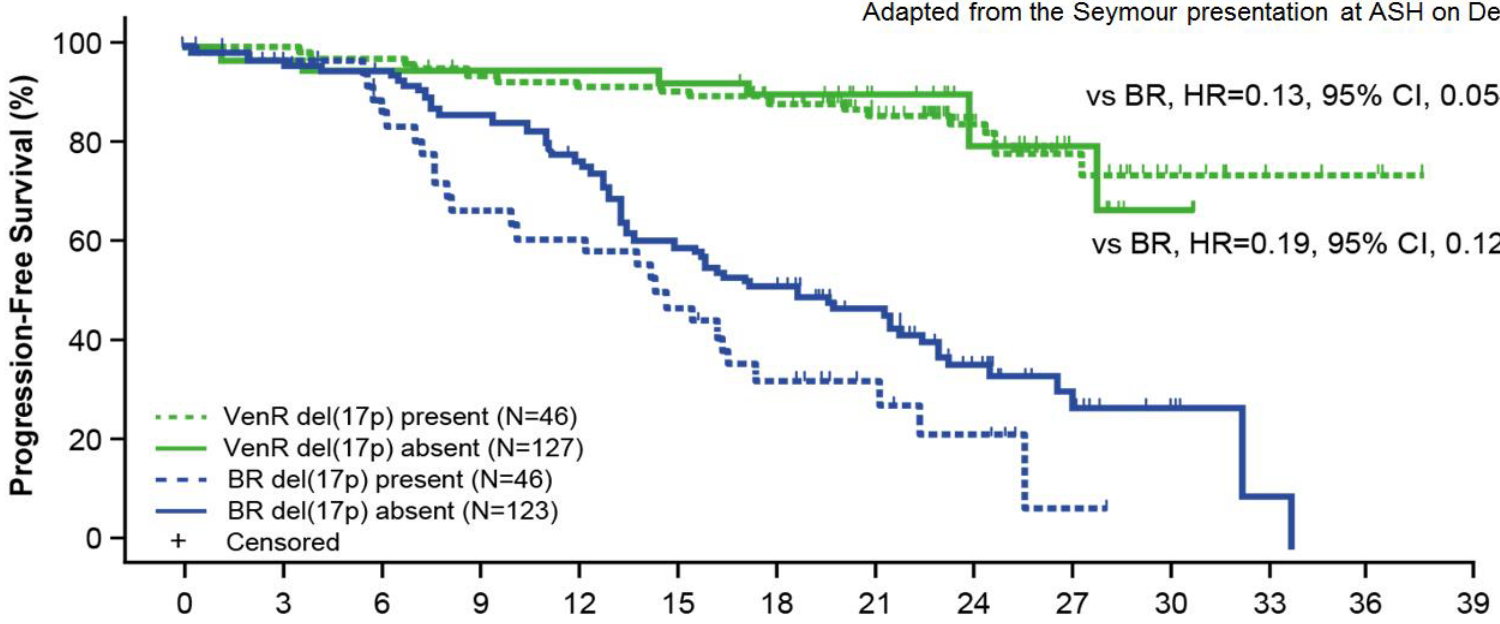


Adapted from the Seymour presentation at ASH on December 12, 2017

As of 8 May 2017

Investigator-assessed PFS Superior for VenR vs. BR Among Patients With and Without del(17p)

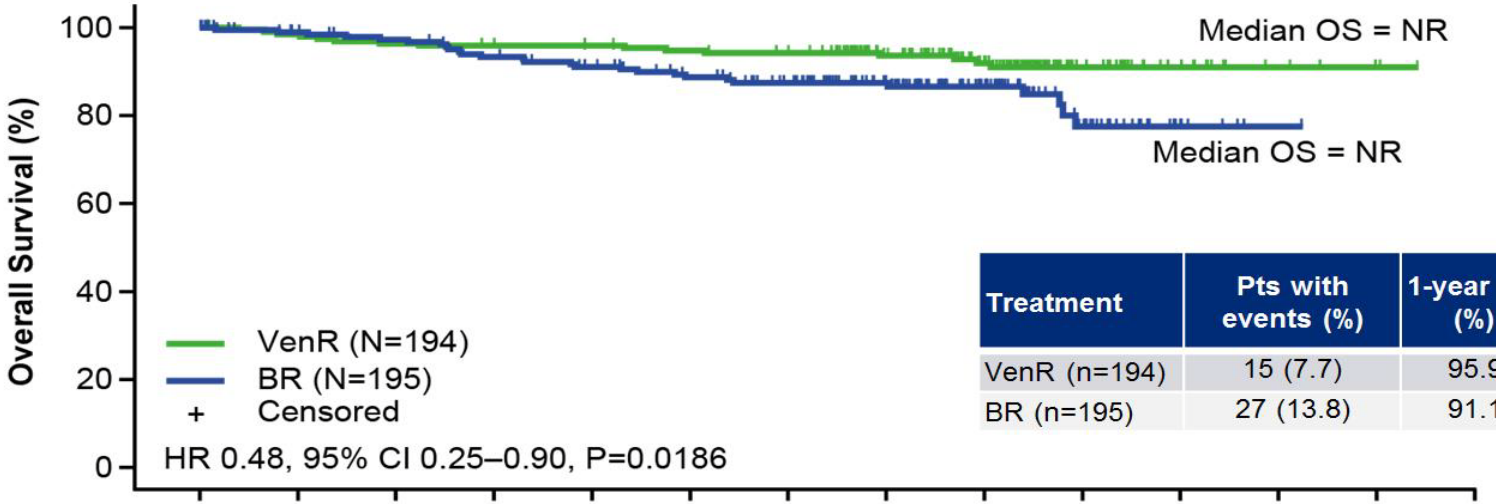
Adapted from the Seymour presentation at ASH on December 12, 2017



No. of patients at risk:													
VenR del(17p) present	46	44	43	43	43	42	36	25	17	7	2		
VenR del(17p) absent	127	127	124	118	116	114	105	76	48	20	10	4	3
BR del(17p) present	46	40	34	27	25	20	14	8	5	1			
BR del(17p) absent	123	114	108	99	88	70	60	44	26	10	3	1	

As of 8 May 2017

Clinically Meaningful Improvement in Overall Survival for VenR vs. BR



Treatment	Pts with events (%)	1-year OS (%)	2-year OS (%)
VenR (n=194)	15 (7.7)	95.9	91.9
BR (n=195)	27 (13.8)	91.1	86.6

No. of patients at risk:

VenR	194	190	185	183	181	178	175	142	102	36	15	5	3
BR	195	181	175	166	158	146	134	102	66	29	8	2	

Descriptive p-values
Pre-specified boundary, P=0.0001.

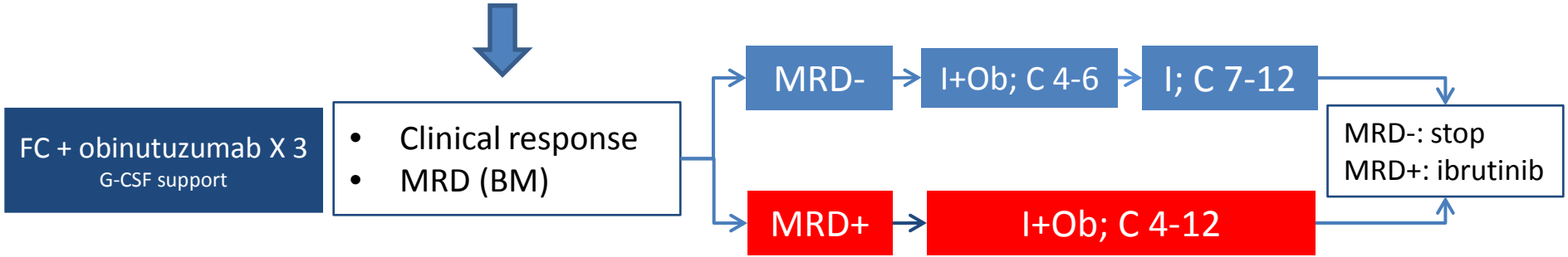
Adapted from the Seymour presentation at ASH on December 12, 2017

As of 8 May 2017

New combinations for First line treatment of CLL

Ibrutinib	with chemo	with FCR
		with bendamustine
	chemo sparing strategy	with obinutuzumab/ofatumumab
		with rituximab
Venetoclax	chemo sparing strategy	with obinutuzumab
		with ibrutinib

Ibrutinib, Fludarabine, Cyclophosphamide, and Obinutuzumab (GA101) (iFCG) for First-Line Treatment of Patients with CLL with **Mutated *IGHV*** and **without *TP53* aberrations**



Eligibility criteria
- age ≥18,
- IGHV-M,
- no del(17p)/TP53 mutation

Primary endpoint
CR/CRi and
undetectable BM MRD after 3 courses of iFCG
(4-color flow-cytometry, sensitivity 10^{-4})

I: ibrutinib, Ob: Obinutuzumab G:GA101; C:cycle; *by 4-color flow, sensitivity 10^{-4})

Jain N et al, MDACC abs#495, ASH 2017 NCT02629809

iFCG for First-Line Treatment of Patients with CLL with Mutated IGHV and without TP53 abn
Efficacy in 32 patients (median follow-up 10.9 months)

Table 1

	N (%) or median [range] N=32	
Age, yrs	60 [25-71]	
Gender, M	26 (81)	
FISH	del(13q)	23 (72)
	Trisomy 12	6 (19)
	Negative	3 (9)
WBC, K/µL	58.7 [2.4-224]	
Platelet, K/µL	116 [62-292]	
Hemoglobin, g/dL	12.1 [8.5-15.6]	
B2M, mg/L	2.6 [1.4-8.1]	
Karyotype (n=27)	Diploid	17 (63)
	del(13q)	6 (22)
	Trisomy 12	4 (15)

Table 2

	Response at 3 Months (N=28)		Best Response (N=28)	
		BM MRD		BM MRD
ORR	28 (100)	24/28 (86) neg	28 (100)	All neg
CR/CRi	13 (46)	All neg	22 (78)	All neg
PR	15 (56)	11/15 (73) neg	6 (22)	All neg

Figure 1

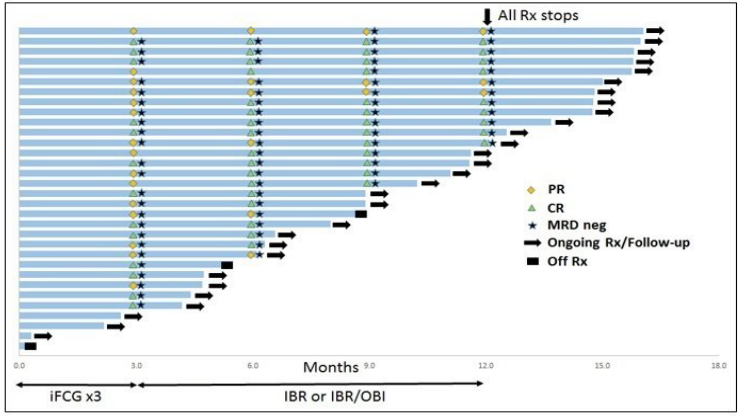


Figure 2

The historical rate of C3 undetectable BM MRD with FCR in IGHV-M pts was 26% (Strati, Blood 2014)

iFCG for First-Line Treatment of Patients with CLL with Mutated IGHV and without TP53 abn
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ORR	28 (100)	24/28 (86) neg	28 (100)	All neg
CR/CRi	13 (46)	All neg	22 (78)	All neg
PR	15 (56)	11/15 (73) neg	6 (22)	All neg

Figure 1

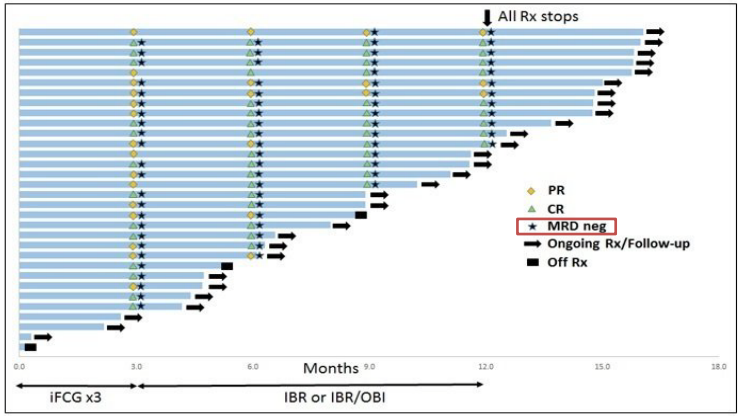
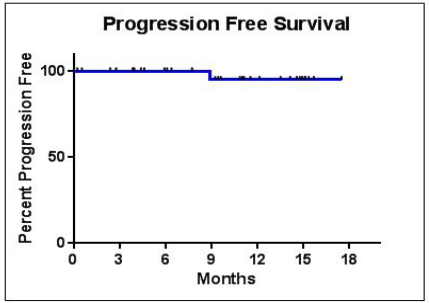


Figure 2



Jain N et al, MDACC abs#495, ASH 2017 NCT02629809

iFCG for First-Line Treatment of Patients with CLL with Mutated IGHV and without TP53 abn

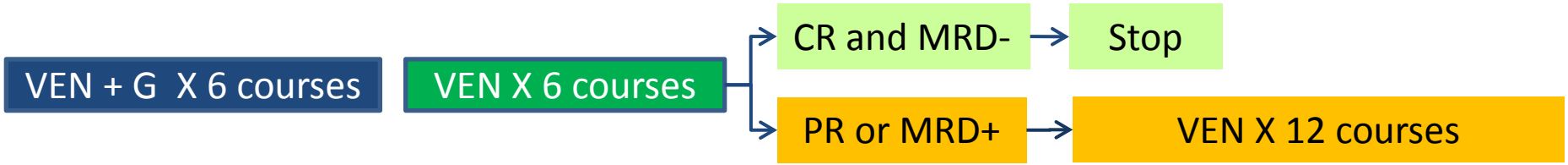
Toxicity in 32 patients (median follow-up 10.9 months)

AE (32 pts)	% of the patients (or n. of patients)
G3-4 neutropenia	68% (G-CSF support mandatory)
G3-4 thrombocytopenia	48%
Atrial fib	2 patients
G3 ALT elevation	3 patients
Dose reductions	
- FC	55%
- ibrutinib	19%
Premature discontinuation	
- G3 IRR and G4 thrombocytopenia	1 patient
- Death*	1 patient

*This was a 26 year old patient with no cardiac history who developed new onset congestive heart failure during cycle 9 of treatment with ibrutinib and obinutuzumab.

Jain N et al, MDACC abs#495, ASH 2017 NCT02629809

Safety, Efficacy and MRD Negativity of a Combination of Venetoclax and Obinutuzumab in Patients with Previously Untreated CLL – Results from a Phase 1b Study (GP28331)



Eligibility criteria

- 1L CLL
- ECOG PS ≤1,
- adequate organ function
- need of treatment

Endpoints

- safety and tolerability
- efficacy
- MRD negativity (PB and BM)

Flinn IW et al oral presentation abs # 430 – ASH 2017 - ClinicalTrials.gov Identifier: NCT01685892
Nashville, TN; Barts Cancer Institute; MDACC; Weill Cornell Medicine, New York, NY; OSU; St James's University Hospital, Leeds UCSM;

Efficacy and Safety of a Combination of Venetoclax and Obinutuzumab in Patients with Previously Untreated CLL – Results from a Phase 1b Study (GP28331)

- 32 1L pts enrolled and followed for ≥9 mo.
- Median age 63.0 y (range 47.0–73.0)
- 5 pts (15%) 17p- / 6 pts (18%) 11q-
- Median time on study: 11.3 mo (10.0–23.0)

- No discontinuations of treatment due to AEs
- No clinical TLS
- No treatment-related death
- No high-grade infusion related reactions

Table 1. Summary of AEs

Adverse Events	Total (N=32)
AEs of any grade in ≥25% of total pts, n (%)	
Any infectious AE	22 (68.8)
Nausea	21 (65.6)
Infusion-related reaction*	18 (56.3)
Diarrhea	16 (50)
Neutropenia	17 (53.1)
Pyrexia	15 (46.9)
Fatigue	14 (43.8)
Headache	12 (37.5)
Chills	11 (34.4)
Thrombocytopenia	11 (34.4)
Vomiting	11 (34.4)
Anemia	10 (31.3)
Cough	10 (31.3)
Flushing	10 (31.3)
Dyspnea	9 (28.1)
Constipation	8 (25)
Grade 3–4 AEs occurring in ≥2 total pts	
Neutropenia	13 (40.6)
Febrile neutropenia	4 (12.5)
Thrombocytopenia	4 (12.5)
Anemia	3 (9.4)

*Signs and symptoms of infusion-related reactions could be captured as separate AEs

Flinn IW et al oral presentation abs # 430 – ASH 2017

Response, PB / BM negativity rates and PFS

- Overall response rate 100%
- CR/CRi 56.3%
- PFS 100% at 1 yr
- 2 pts (6.3%) progressed at d 437 and d 451
  Both had del(17p)
  Both maintained BM MRD positivity at 1 yr

PB MRD- (ITT)	N. of patients (%)
Best MRD-	32/32 (100%)*
≥3 mo after last G	27/32 (84%)**
≥9 mo after last G	10/12 (83%)
BM MRD- (ITT)	20/32 (62,5%)***
BM MRD- (in samples available)	20/27 (74)

MRD negativity (<1 CLL cell detectable per 10,000 leukocytes)
MRD negativity was assessed by 5-color flow cytometry

*2 pts converted to MRD+ 3 mo after last G dose; ** in 5 pts the PB sample was NA
*** in 5 pts the BM sample was NA

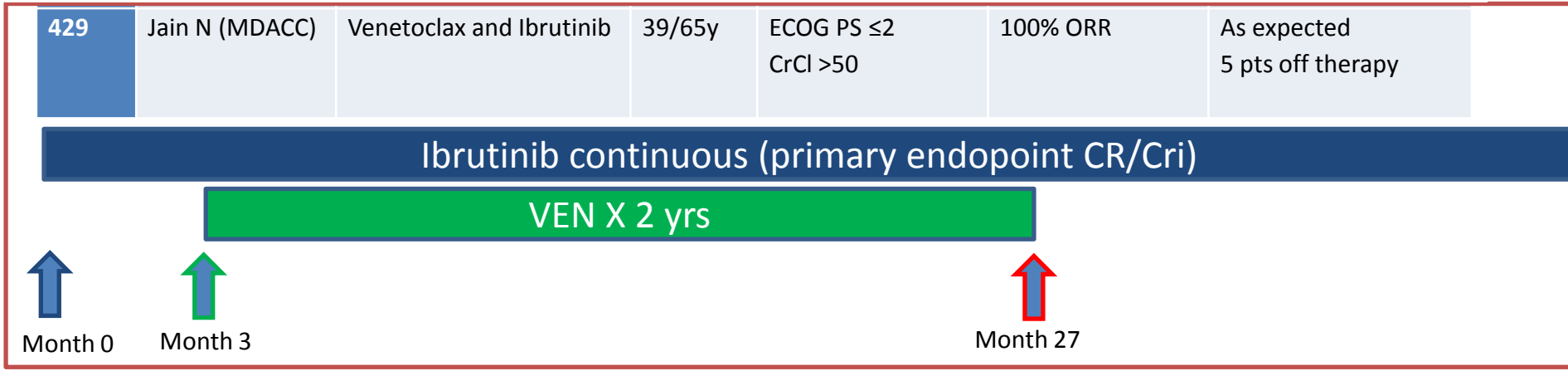
Flinn IW et al oral presentation abs # 430 – ASH 2017

Combination between venetoclax and ibrutinib in treatment-naïve CLL (oral communications)

Abs N.	Author/Centre	Combination	N. Of patients/ median age (y)	Inclusion criteria	Efficacy	Toxixity
431	Rogers KA (OSU)	Obinutuzumab, Ibrutinib, and Venetoclax	25/59y	ECOG PS ≤1 CrCl ≥50	CR+Cri 50% MRD-(BM) 58%	As expected
429	Jain N (MDACC)	Venetoclax and Ibrutinib	39/65y	ECOG PS ≤2 CrCl >50	100% ORR	As expected 5 pts off therapy

Combination between venetoclax and ibrutinib in treatment-naïve CLL (oral communications)

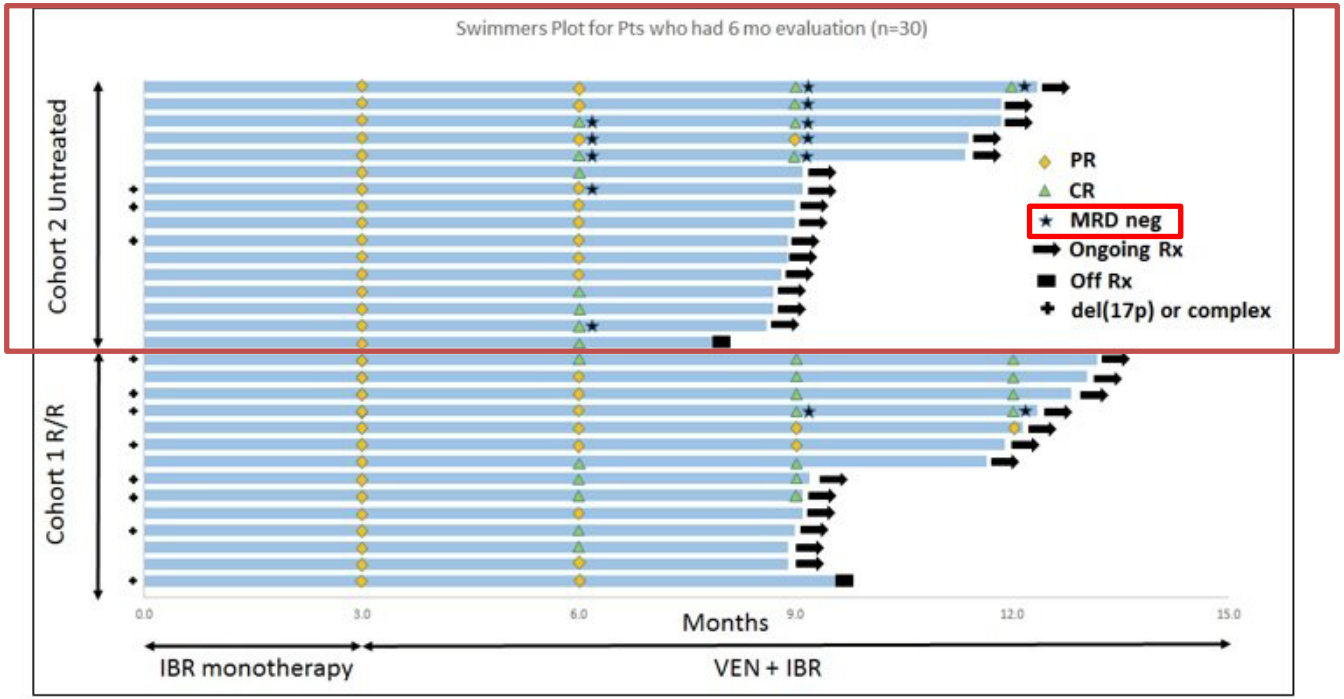
Abs N.	Author/Centre	Combination	N. Of patients/ median age (y)	Inclusion criteria	Efficacy	Toxixity
429	Jain N (MDACC)	Venetoclax and Ibrutinib	39/65y	ECOG PS ≤2 CrCl >50	100% ORR	As expected 5 pts off therapy



16 TREATMENT-NAIVE PATIENTS WHO COMPLETED 6 MO EVALUATION

- 15/16 on treatment
- 9/16 CR
- 7/16 MRD negative

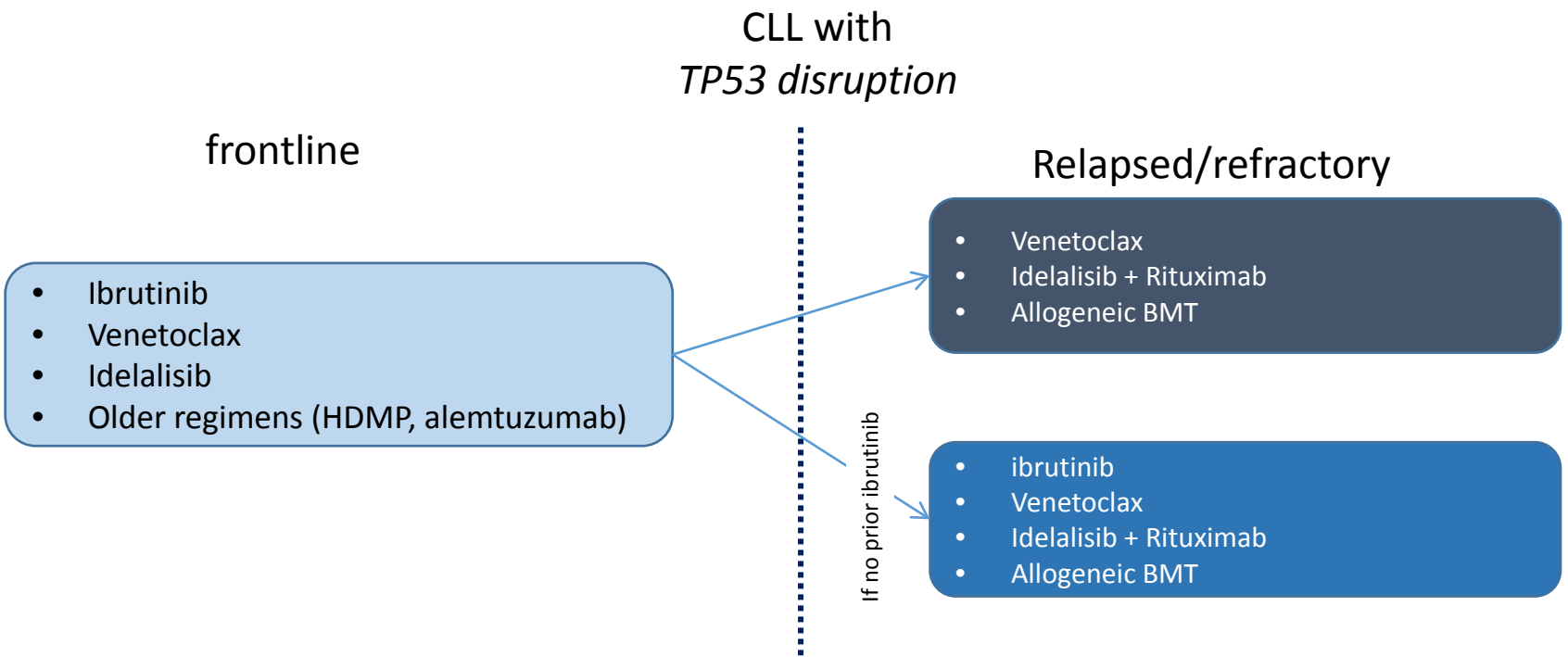
Figure



Jain N et al, abs # 429 – ASH 2017

How should we sequence and combine novel therapies in CLL?

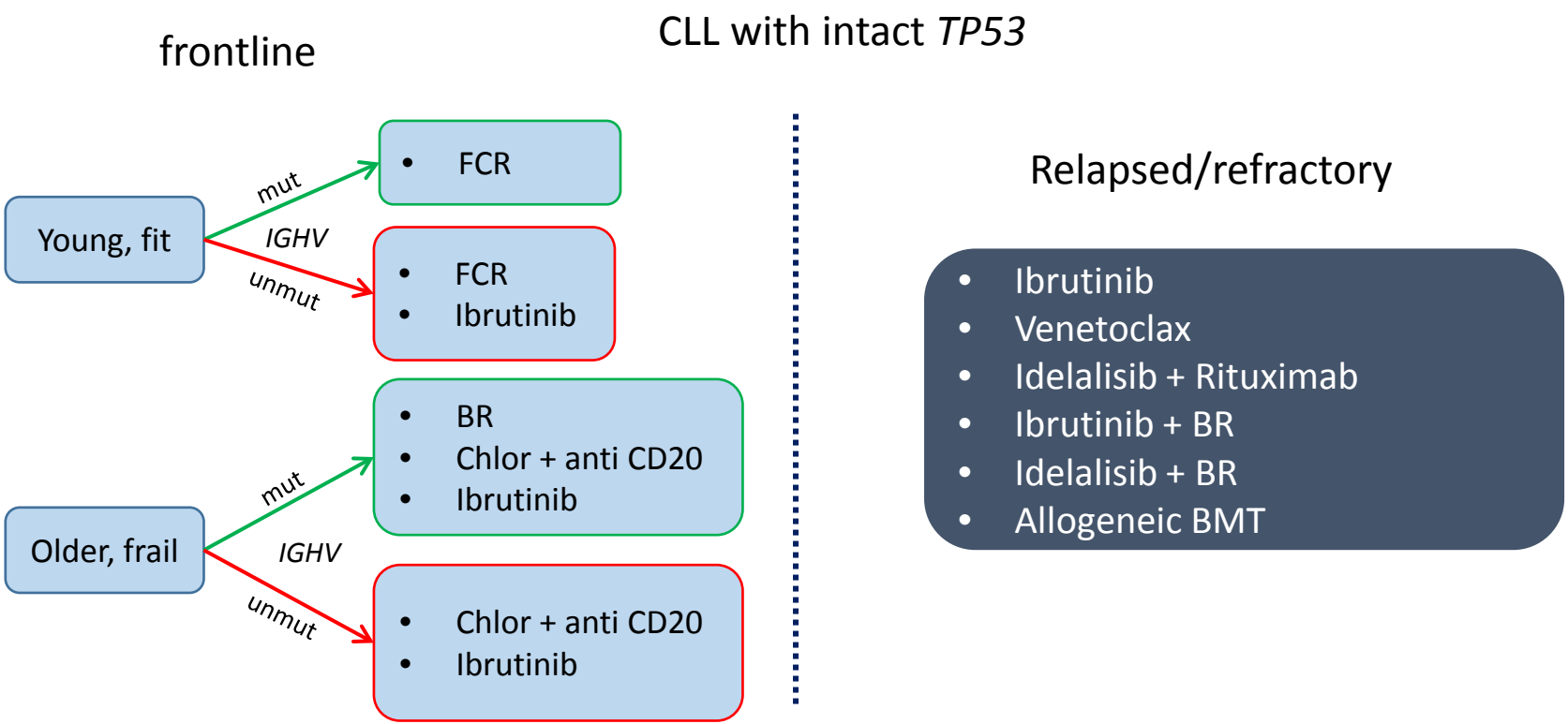
Current treatment options



Modified from Davids MS. Hematology Am Soc Hematol Educ Program. 2017 Dec 8;2017(1):346-353.

How should we sequence and combine novel therapies in CLL?

Current treatment options



Davids MS. Hematology Am Soc Hematol Educ Program. 2017 Dec 8;2017(1):346-353.